BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

REMARKS

No amendments have been made. Claims 1-20 are currently pending in the captioned application.

Anticipation Rejection

Claims 1-8, 10, and 17-20 were rejected under 35 USC §102(a) as anticipated by WO 01/21155 A1 ("Remon"). (Paper No. 20040220 at 2.)

For the reasons set forth below, the rejection, respectfully is traversed.

Remon discloses

(57) Abstract: Biologically inactive cushioning beads comprise at least one compressible cushioning component consisting essentially of a microcrystalline hydrocarbon wax or a natural wax, the said wax being at least 30 % by weight of the biologically inactive cushioning beads. Such beads are useful for making solid shaped articles containing biologically active ingredients by compression.

The formulation of a solid oral dosage form, whether tablet or capsule, which disintegrates rapidly in water to form an instantaneous homogenous suspension of adequate viscosity to be swallowed could circumvent the problems of administering large dosages without premature release from controlled-release particles while providing a ready measured dose. The key to the development of such a dosage form is a rapidly disintegrating tablet which disperses to form a viscous suspension. A delay in the development of a viscous gel is essential for achieving disintegration of the tablet. On the

p. 1

properties.

The ideal solid oral dosage form should contain a swellable material which is able to increase viscosity on contact with water, at least one biologically active ingredient for immediate or sustained release delivery of the biologically active ingredient, and a filler conferring compactibility and the capability to disintegrate quickly. The inclusion of a viscosity increasing agent as a fine powder in the tablet matrix without any processing would interfere with disintegration and result in the formation of a voluminous hydrophilic mass which is impossible to disperse. Thus, it is necessary to incorporate such an agent into the tablet as granules or spheres so that the disintegration process occurs before the viscosity increase.

p. 2

The present invention may provide biologically inactive cushioning beads comprising at least one compressible cushioning component consisting essentially of a microcrystalline hydrocarbon wax or a natural wax, the said wax being at least about 30% by weight of the biologically inactive cushioning beads and which are useful for making solid shaped articles containing biologically active ingredients by compression.

p. 10

For the performance of the present invention, it is prefcrablc to usc a microcrystalline hydrocarbon wax having a congealing point between about 50°C and 90°C and which is water-insoluble. The microcrystalline hydrocarbon wax usually comprises a mixture of linear (normal) and branched (iso) hydrocarbons, According to a preferred embodiment of the present invention, the said mixture comprises from about 30 to about 90% by weight of linear hydrocarbons and from about 10 to about 70% by weight of branched hydrocarbons. Also preferably, the microcrystalline hydrocarbon wax

p. 12

flavoring agent (e.g. vanillin), buffering agent, filler, disintegrating agent and/or swellable material. Preferably the cushioning beads of the present invention include at least about 5% by weight of at least one such biologically inactive pharmaceutically acceptable additive (excipient) distributed throughout the beads, for instance in the form of an intimate mixture of wax and excipient. A disintegrating agent is especially useful as an excipient for providing quick-disintegrating characteristics when making a solid shaped article containing biologically active ingredients by compression.

p. 15

In making the rejection, the Examiner contended that

- "Remon teaches a rapidly disintegrating tablet comprising an active agent and wax particles." (Paper No. 20040220 at 2.)
- The wax is a microcrystalline wax or a natural wax. (*Id.*)
- The "composition further contains disintegrants, swellable materials as well as other fillers." (*Id.* at 3.)
- The wax particles have an average particle size of 0.5 to 2.0 mm. (*Id.*)
- The actives are chosen from a wide variety of known pharmaceutical agents. (*Id.*)
- The composition includes a film coating. (*Id.*)
- The tablets are produced by compression. (*Id.*)
- The tablets are rapid disintegration tablets. (*Id.*)

The Examiner admitted that "Remon does not refer to wax particles as powder." To fill the acknowledged gap, the Examiner looked to a dictionary definition for powder. Based on that definition the Examiner reasoned that since the claims of the captioned application "do not recite a particle size for the wax particles, the instant claims are deemed anticipated by Remon." (*Id.*)

As is well settled, anticipation requires "identity of invention." Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim.

Initially, we note that there must be no difference between what is claimed and what is disclosed in the applied reference. "Moreover, it is incumbent upon the Examiner to ***identify wherein each and every facet*** of the claimed invention is disclosed in the applied reference." The Examiner is required to point to the disclosure in the reference "***by page and line***" upon which the claim allegedly reads.

The rejection failed to identify where in Remon each and every element of claims 1-8, 10, and 17-20 are shown. In particular, the Examiner failed to identify where in Remon there is a specific disclosure of an immediate release tablet meeting the USP dissolution specification for immediate release tablets containing the active ingredients disclosed in Remon.

For example, the rejection stated that "Remon teaches **a rapidly disintegrating** tablet." In contrast, the rejected claims require, among other things, **an immediate release** tablet as demo. Based on this, it appears that the Examiner may not appreciate the difference between an immediate release table meeting the USP **dissolution** specifications for immediate release tablets containing said active ingredient and **disintegration** as disclosed in Remon.

Attached hereto as Exhibit A is copy of Chapter 34: DISSOLUTION from Remmington: The Science and Practice of Pharmacy (19th ed.) pp. 593-604 (Mack Publishing Company 1995). In particular, the Examiner's attention is directed to the left-hand column of page 595 of Exhibit A wherein it is explicitly stated that "In general, however, disintegration has proved to be a poor indicator of bioavailability ... Several factors... have been found to affect dissolution of the drug substance but have no relevance to disintegration." (Emphasis added.) Thus it appears from this treatise that,

while the disintegration and dissolution may share a common "S"-shaped curve, dissolution does not necessarily correlate to disintegration. In other words, just because tablet may rapidly disintegrate does not mean that the tablet is an immediate release tablet that meets the USP dissolution specifications for immediate release tablets containing the active ingredient. Because the Examiner appears to correlate disintegration with dissolution, the rejection is improper and should be withdrawn.

Even if the Examiner were to maintain the Office's position in this record, which is disagreed with for the reasons set forth above, the Examiner is asked to consider the dissolution profiles of tablets disclosed in Examples 5 and 6 of Remon. These profiles are depicted in Figs. 6 and 7 of Remon. While there is no indication that these experiments were conducted following the USP dissolution specifications for diltiazem immediate release tablets, the data does show that "a dissolution percentage of at least 80% is readily achievable within 8 hours." (Remon at p. 28, lns. 5-6 and 15-16.)

First, it is not seen where either of these profiles would be considered an "immediate release" tablet under any suitable definition of "immediate release." Second, the dissolution profile for acetaminophen attached to the November 12, 2003 shows a dissolution profile wherein not less than 80% is dissolved in 30 minutes. Thus, it is not seen where the Examiner has satisfied the required burden of proof as to where each and every element of the claimed invention is disclosed and identically arranged in Remon. For this additional reason, the rejection is improper and should be withdrawn.

Obviousness Rejection

Claims 9 and 6 were rejected under 35 USC §103(a) as being unpatentable over Remon. (Paper No. 20040220 at 4.)

For the reasons set forth below the rejection, respectfully is traversed.

Remon's disclosure set forth above is incorporated herein by reference.

In making the rejection, the Examiner incorporated the assertions set forth in the anticipation rejection above into the instant rejection. The Examiner acknowledged, however, that Remon "does not expressly teach the same concentration of wax or active agent or the same particle size for the wax particles." (Paper No. 20040220 at 4.)

To fill the acknowledged gap, the Examiner relied upon the assumption that such "limitations would be routinely determined by one of ordinary skill in the art, through

minimal experimentation, as being suitable, absent the presentation of some unusual and/or unexpected results." (*Id.* at 4).

The Examiner then concluded that, "it would have been obvious to a person of ordinary skill in the art to vary concentrations and particle [sic] sizes in tablet formulations" "to prepare similar tablets with different active agents that achieve the goal of rapid disintegration." (*Id.*.)

Initially, it is noted that rejected claims are silent as to any requirement for "rapid disintegration." From the Examiner's reasoning it appears that the Examiner is relying on "rapid disintegration" as being an affirmative claim limitation. Such reliance on a disclosure found in Remon but not in the rejected claims is evidence that the Examiner has used hindsight to pick and choose parts of a cited document to make the rejection rather than rely the entire cited documents. For this reason, the rejection is improper and should be withdrawn.

For a *prima facie* case of obviousness to be established, the teachings from the prior art itself must appear to have suggested the claimed subject matter to one of ordinary skill in the art. The mere fact that the prior art could be modified as proposed by the Examiner is not sufficient to establish a *prima facie* case of obviousness.

Additionally, the Examiner may not appreciate the difference between an immediate release tablet meeting the USP **dissolution** specifications for immediate release tablets containing said active ingredient and **disintegration** as disclosed in Remon.

The Examiner is again directed Exhibit A and to the left-hand column of page 595 therein wherein it is explicitly stated that "[I]n general, however, disintegration has proved to be a poor indicator of bioavailability ... Several factors... have been found to affect dissolution of the drug substance but have no relevance to disintegration." (Emphasis added.) Thus it appears from this treatise that, while the disintegration and dissolution may share a common "S"-shaped curve, dissolution does not necessarily correlate to disintegration. In other words, just because a tablet may rapidly disintegrate does not mean that the tablet is an immediate release tablet that meets the USP dissolution specifications for immediate release tablets containing the active ingredient. It is not seen where a disclosure of a rapid disintegrating tablet would suggest an

immediate release tablet of the rejected claims. Because disintegration and dissolution are not the same and because there does not appear to be any suggestion by the Examiner that would lead one of ordinary skill in the art to formulate the claimed subject matter based on the current record in the captioned application, the rejection is improper and should be withdrawn.

Even if the Examiner were to maintain the Office's position in this record, which is disagreed with for the reasons set forth above, the Examiner is asked to consider the dissolution profiles of tablets disclosed in Examples 5 and 6 of Remon. These profiles are depicted in Figs. 6 and 7 of Remon. While there is no indication that these experiments were conducted following the USP dissolution specifications for diltiazem immediate release tablets, the data does show that "a dissolution percentage of at least 80% is readily achievable within 8 hours." (Remon at p. 28, lns. 5-6 and 15-16.)

First, it is not seen where either of these profiles would be considered an "immediate release" tablet under any suitable definition of "immediate release." Second, the dissolution profile for acetaminophen attached to the November 12, 2003 shows a dissolution profile wherein not less than 80% is dissolved in 30 minutes. Thus, it is not seen where the Examiner has satisfied the required burden of proof required to make out a prima facie case of obviousness. For this additional reason, the rejection is improper and should be withdrawn.

Claims 11-15 were rejected under 35 USC §103(a) as being unpatentable over Remon in combination with US Pat. No. 5,494,681 ("Cuca"). (Paper No. 20040220 at 4.)

For the reasons set forth below the rejection, respectfully is traversed.

Remon's disclosure set forth above is incorporated herein by reference.

Cuca discloses a tastemasked system by casting or spin congealing melt dispersions and/or solutions of drug or other active material, or combinations of drugs or medicaments in a molten blend of materials. (Col. 2, lns. 64-67.) Cuca further discloses that a substantially tasteless pharmaceutical delivery system is formed which comprises: (a) an active material or a combination of drugs or medicaments; and (b) a spatially oriented matrix comprising (i) a major amount of wax core material having a melting

point within the range of about 50°C. and about 200°C.; and (ii) a minor amount of a hydrophobic polymer material. (Col. 3, lns. 1-6 and 56.)

In making the rejection, the Examiner incorporated the assertions set forth above in the anticipation rejection into the instant rejection. The Examiner acknowledged, however, that Remon "does not expressly teach including a second active agent." (Paper No. 20040220 at 4.)

To fill the acknowledged gap, the Examiner looked to Cuca as "teach[ing] that tablet formulations can comprise one or more active agents."

The Examiner reasoned that one of ordinary skill in the art would have been motivated to use more than one active agent "to provide a composition that better delivers a therapeutic dose to the host to better combat the disease or condition being treated." (*Id. at 5.*) The Examiner then concluded that "at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to prepare a tablet formulation with one or more active agents incorporated into the composition. (*Id.*)

Initially, it is noted that rejected claims are silent as to any requirement for "rapid disintegration." From the Examiner's reasoning it appears that the Examiner is relying on "rapid disintegration" as being an affirmative claim limitation. Such reliance on a disclosure found in Remon but not in the rejected claims is evidence that the Examiner has used hindsight to pick and choose parts of a cited document to make the rejection rather than rely on the entire documents. For this reason, the rejection is improper and should be withdrawn.

For a *prima facie* case of obviousness to be established, the teachings from the prior art itself must appear to have suggested the claimed subject matter to one of ordinary skill in the art. The mere fact that the prior art could be modified as proposed by the Examiner is not sufficient to establish a *prima facie* case of obviousness.

Additionally, the Examiner may not appreciate the difference between an immediate release tablet meeting the USP **dissolution** specifications for immediate release tablets containing said active ingredient and **disintegration** as disclosed in Remon.

The Examiner is again directed toExhibit A and to the left-hand column of page 595 therein wherein it is explicitly stated that "[I]n general, however, disintegration has

proved to be a poor indicator of bioavailability ... Several factors... have been found to affect dissolution of the drug substance but have no relevance to disintegration." (Emphasis added.) Thus it appears from this treatise that, while the disintegration and dissolution may share a common "S"-shaped curve, dissolution does not necessarily correlate to disintegration. In other words, just because tablet may rapidly disintegrate does not mean that the tablet is an immediate release tablet that meets the USP dissolution specifications for immediate release tablets containing the active ingredient. It is not seen where a disclosure of a rapid disintegrating tablet would suggest an immediate release tablet of the rejected claims.

Cuca does not close the gap between the disintegration disclosed in Remon and the dissolution requirements of the claimed subject matter.

Because disintegration and dissolution are not the same and because there does not appear to be any suggestion by cited documents that would lead one of ordinary skill in the art to formulate the claimed subject matter based on the current record in the captioned application, the rejection is improper and should be withdrawn.

Even if the Examiner were to maintain the Office's position in this record, which is disagreed with for the reasons set forth above, the Examiner is asked to consider the dissolution profiles of tablets disclosed in Examples 5 and 6 of Remon. These profiles are depicted in Figs. 6 and 7 of Remon. While there is no indication that these experiments were conducted following the USP dissolution specifications for diltiazem immediate release tablets, the data does show that "a dissolution percentage of at least 80% is readily achievable within 8 hours." (Remon at p. 28, lns. 5-6 and 15-16.)

First, it is not seen where either of these profiles would be considered an "immediate release" tablet under any suitable definition of "immediate release." Second, the dissolution profile for acetaminophen attached to the November 12, 2003 shows a dissolution profile wherein not less than 80% is dissolved in 30 minutes. Additionally, it is not seen where Cuca would close the gaps left by Remon. Thus, it is not seen where the Examiner has satisfied the required burden of proof required to make out a prima facie case of obviousness. For this additional reason, the rejection is improper and should be withdrawn.

Finally, the Examiner is invited to call the applicants' undersigned representative if any further action will expedite the prosecution of the application or if the Examiner has any suggestions or questions concerning the application or the present Response. In fact, if the claims of the application are not believed to be in full condition for allowance, for any reason, the applicants respectfully request the constructive assistance and suggestions of the Examiner in drafting one or more acceptable claims pursuant to MPEP §707.07(j) or in making constructive suggestions pursuant to MPEP §706.03 so that the application can be placed in allowable condition as soon as possible and without the need for further proceedings.

Respectfully submitted,

By: _____
Timothy E. Tracy
Reg. No. 39,401

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-6586
DATE: June 25, 2004

EXHIBIT "A"

Remington: The Science and Practice of Pharmacy

Volume I

19TH
EDITION

Remington: Practice of

ALFONSO R GENNARO

Chairman of the Editorial Board
and Editor

The Science and Pharmacy

1995

MACK PUBLISHING COMPANY
Easton, Pennsylvania 18042

Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

The use of structural formulas from USAN and the USP Dictionary of Drug Names is by permission of The USP Convention. The Convention is not responsible for any inaccuracy contained herein.

NOTICE—This text is not intended to represent, nor shall it be interpreted to be, the equivalent of or a substitute for the official United States Pharmacopeia (USP) and/or the National Formulary (NF). In the event of any difference or discrepancy between the current official USP or NF standards of strength, quality, purity, packaging and labeling for drugs and representations of them herein, the context and effect of the official compendia shall prevail.

Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

CHAPTER 34

Dissolution

Hamed M Abdou, PhD
Vice President
Quality Control and Quality Assurance
Bristol-Myers Squibb
Pharmaceuticals Group
New Brunswick, NJ 08903

Dissolution is the process by which a solid of only fair solubility characteristics enters into solution. The earliest reference to dissolution is probably an article by Noyes and Whitney in 1897, about "The Rate of Solution of Solid Substances in Their Own Solution." The authors suggested that the rate of dissolution of solid substances is determined by the rate of diffusion of a very thin layer of saturated solution that forms instantaneously around the solid particle. They developed the mathematical relationship that correlates the dissolution rate to the solubility gradient of the solid. Their equation is still the basic formula upon which most of the modern mathematical treatments of the dissolution phenomenon revolve.

Noyes and Whitney's work however, as well as most of the work which has been conducted during the first part of this century, was concentrated on the study of the physicochemical aspects of dissolution as applied to chemical substances. Most important of these studies were the application of Fick's law of diffusion to the Noyes and Whitney equation by Nernst and Brunner in 1904, and the development of the famous *Cubic Root Law* of dissolution by Hixson and Crowell in 1931.

At the middle of the century, emphasis started to shift to the examination of the effects of dissolution behavior of drugs on the biological activity of pharmaceutical dosage forms. One of the earliest studies with this purpose in mind was conducted by J Edwards in 1951 on aspirin tablets. Based on his findings, he reported that "because of its poor solubility, the analgesic action of aspirin tablets would be controlled by its dissolution rate within the stomach and the intestine." No *in vivo* studies, however, were conducted by Edwards to support his postulate.

About 8 years later, Shenoy *et al* proved the validity of Edward's suggestion of the *in vitro/in vivo* correlation by demonstrating a direct relationship between the bioavailability of amphetamine from sustained release tablets and its *in vitro* dissolution rate. Other studies, especially those reported by Nelson, Levy and others, confirmed beyond doubt, the significant effect of the dissolution behavior of drugs on their pharmacological activities. Because of the importance of these findings, dissolution testing began to emerge as a dominant topic within both the pharmaceutical academia and the drug industry.

In the late 1960s dissolution testing became a mandatory requirement for several dosage forms. The role of dissolution in the absorption of drug products, however, still is far from being understood perfectly. In spite of the reported success of several *in vitro/in vivo* correlation studies, dissolution is not a predictor of therapeutic efficiency. Rather, it is a qualitative tool which can provide valuable information about the biological availability of a drug as well as batch-to-batch consistency. Another area of difficulty is the fact that the accuracy and precision of the testing procedure is dependent, to a large extent, on the strict observance of so many subtle parameters and detailed operational controls.

In spite of these shortcomings, dissolution is considered today as one of the most important quality-control tests performed on pharmaceutical dosage forms. For a comprehensive treatment, the reader is referred to the text of Abdou.[1]

Theory of Dissolution

Diffusion-Layer Model (Film Theory)

In 1897, Noyes and Whitney studied the dissolution rate of benzoic acid and lead chloride, two practically insoluble substances, by rotating a cylinder of each compound in water at a constant rate and sampling the solution for analysis at specific time intervals. In order to examine their data quantitatively, Noyes and Whitney developed an equation based on Fick's second law, to describe the dissolution phenomenon

$$\frac{dc}{dt} = K(c_s - c_t) \qquad (1)$$

where dc/dt is the dissolution rate of the drug, K is the proportionality constant, c_s is the saturation concentration (maximum solubility), c_t is the concentration at time t and $c_s - c_t$ is the concentration gradient. The proportionality constant, K, also is called the dissolution constant and the equation has been shown to obey first order kinetics (Fig 1).

In their experiments, Noyes and Whitney maintained a constant surface area by using sticks of the insoluble substance. However, because such a condition is not always applicable, Brunner and Tolloczko modified Eq 1 to incorporate the surface area, S, as a separate variable.

$$\frac{dc}{dt} = k_1 S(c_s - c_t) \qquad (2)$$

In order to explain the mechanism of dissolution, Nernst in 1904 proposed the film-model theory. Under the influence of no reactive or chemical forces, a solid particle immersed in a liquid, undergoes two consecutive steps: (1) the solution of the solid at the interface, forming a thin stagnant layer or film, h, around the particle and (2) the diffusion from this layer at the boundary to the bulk of the fluid. The first step, solution, is almost instantaneous; the second, diffusion, is much slower and, therefore, is the rate-limiting step (see Fig 1).

In the same year, Brunner was investigating factors other than surface area that affect the dissolution process in order to determine the fundamental components of the proportionality constant in Eq 1. By using Fick's first law of diffusion and Nernst's newly proposed film theory, Brunner expanded Eq 2 to include the diffusion coefficient, D, the thickness of the stagnant diffusion layer, h, and the volume of the dissolution medium, v, producing

$$\frac{dc}{dt} = k_2 \frac{DS}{vh}(c_s - c_t) \qquad (3)$$

The proportionality constant k_2 is known as the intrinsic dissolution rate constant and is characteristic of each chemical compound.

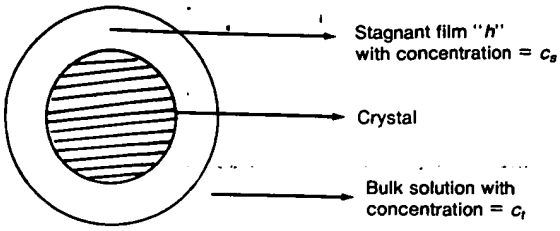

Fig 1. Diffusion-layer model (film theory).

Sink Condition

The term *sink* condition originated from a fact long known by pharmacologists that the drug concentration on both sides of the epithelial layer of the intestinal wall approaches equilibrium in a short time, and that the gastrointestinal tract acts as a *natural sink*; ie, the drug is absorbed instantaneously the moment it dissolves. Therefore, under *in vivo* conditions, there is no concentration buildup and, hence, the retarding effect of the concentration gradient on the dissolution rate, as predicted by Eq 1, does not occur.

In order to simulate the *in vivo* sink condition, *in vitro* dissolution testing usually is conducted using either a large volume of dissolution medium or a mechanism by which the dissolution medium is replenished constantly with fresh solvent at a specified rate so that the concentration of the solute never reaches more than 10 to 15% of its maximum solubility. If such a parameter is maintained, the dissolution testing is said to be conducted under *sink* conditions, ie, under no influence of the concentration gradient. This can be seen from the following mathematical treatment.

Assuming that $c_s \gg c_t$, Eq 3 becomes

$$\frac{dc}{dt} = k_2 \frac{DS}{vh} c_s \qquad (4)$$

As c_s and D are constants for each specific chemical substance; therefore, they could be incorporated in k_2 and appear in Eq 5 as k_3.

$$\frac{dc}{dt} = k_3 \frac{S}{vh} \qquad (5)$$

If the volume of the dissolution medium and the surface area are kept constant during the duration of the dissolution test, then

$$\frac{dc}{dt} = K \qquad (6)$$

Equation 6 predicts a constant dissolution rate under sink condition and represents a zero-order kinetic process, ie, the concentration of the drug increases linearly with time. Equation 6 also is believed to approximate the *in vivo* condition where the dissolution rate of sparingly soluble drugs plays a fundamental role in determining their bioavailability. Figure 2 presents plots of data that would be expected under sink and nonsink conditions.

Hixson and Crowell Cubic Root Law for Dissolution

In Eq 2, the surface area was considered constant for the duration of the dissolution test. Although this could be achieved by using a nondisintegrating disk of the chemical substance, a technique usually employed for the determination of the intrinsic dissolution rate, the same could not be maintained for a dissolving crystal or a regular solid dosage form where complete disintegration is a priority. Therefore, in order to develop a dissolution equation that is based on a changing surface area, Hixson and Crowell modified Eq 2 to represent the rate of appearance of the solute in the solution

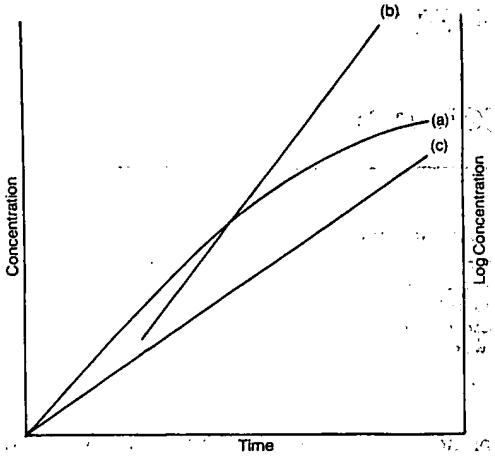

Fig 2. (a) Linear (dissolution rate under nonsink condition) Semi-log first-order kinetic plot of (dissolution rate under non condition); (c) Linear zero-order kinetic plot (dissolution rate u sink condition).

by multiplying each side of the equation by v (volume), le $k_1 v = K$

$$\frac{dW}{dt} = KS(c_s - c_t)$$

where W is the weight of solute in solution.

They also assumed that $S = kw^{2/3}$, where k is a cons containing the shape factor and the density of the particle, w is the weight of undissolved particles at time t.

$$\frac{dW}{dt} = K(kw^{2/3})(c_s - c_t)$$

After mathematical treatments involving the applicatio Fick's first law and integration under the condition that equal to w_o, the initial weight of the particle at time zero, results

$$w_o^{1/3} - w^{1/3} = K_1 t$$

Equation 9 is called the Hixson and Crowell's *Cubic Root* for dissolution.

Theoretical Concepts for the Release of a Drug from Dosage Forms

In determining the dissolution rate of drugs from dosage forms under standardized conditions, one has to sider several physicochemical processes in addition to t previously discussed under dissolution of pure chem substances. These include the wetting characteristics o solid dosage forms, the penetration ability of the dissolu medium into the dosage forms, the swelling process, dis gration and deaggregation. Wagner proposed the schem Fig 3 for the processes involved in the dissolution of dosage forms.

Carstensen explained that the wetting of the solid do

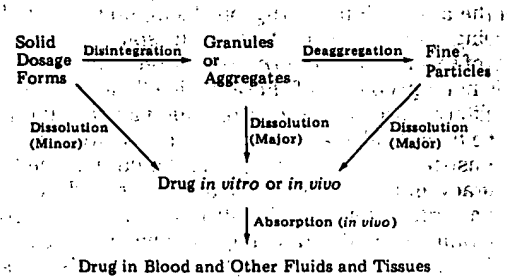

Fig 3. Wagner's schematic diagram illustrating the process volved in the dissolution of solid dosage forms.

form surface controls the liquid access to the solid surface and, many times, is the limiting factor in the dissolution process. The speed of wetting is directly dependent upon the surface tension at the interface (interfacial tension) and upon the contact angle, θ, between the solid surface and the liquid. Generally, a contact angle of more than 90° indicates poor wettability. Incorporation of a surfactant, either in the formulation or in the dissolution medium, lowers the contact angle and enhances dissolution. Also, the presence of air in the dissolution medium causes the air bubbles to be entrapped in the tablet pores and act as a barrier at the interface. For capsules, the gelatin shell is extremely hydrophilic and, therefore, no problems in wettability exist for the dosage itself (although it may exist for the powders inside).

After the solid dosage form disintegrates into granules or aggregates, penetration characteristics play a prime role in the deaggregation process. Hydrophobic lubricants, such as talc and magnesium stearate, commonly employed in tablet and capsule formulations, slow the penetration rate and, hence, the deaggregation process. A large pore size facilitates penetration, but if it is too large it may inhibit penetration by decreasing the internal strain caused by the swelling of the disintegrant.

After deaggregation and dislodgement occur, the drug particles become exposed to the dissolution medium and dissolution proceeds as previously discussed under the Film Theory. Figure 4[2] graphically presents the model proposed by Carstensen.

Correlation Between Disintegration and Dissolution

The close correlation between disintegration and dissolution has been studied by many investigators. Both processes exhibit "S"-shaped curves and a probit or a weibul function were suggested to explain the data. In general, however, disintegration has proved to be a poor indicator of bioavailability because of the turbulent agitation maintained during the test. Several other factors such as solubility, particle size and crystalline structure, among others, have been found to affect the dissolution of the drug substance but have no relevance to disintegration.

Factors Affecting the Rate of Dissolution

Factors that affect the dissolution rate of drug dosage forms can be classified under three main categories.

Factors Relating to the Physiochemical Properties of the Drug

Effect of Solubility on Dissolution—The physicochemical properties of the drug substance play a prime role in controlling its dissolution from the dosage form. The modified Noyes and Whitney equation as expressed in Eq 3 shows that the aqueous solubility of the drug is the major factor which determines its dissolution rate. Actually, some studies showed that drug-solubility data could be used as a rough predictor of the possibility of any future problems with bioavailability, a factor that should be taken into consideration in the formulation design.

Other factors that affect dissolution rate include particle size; crystalline state such as polymorphism and state of hydration, solvation, complexation, as well as surfactants and other reactive additives (acids, bases, buffers, etc). Other physical properties such as density, viscosity and wettability contribute to the general dissolution problems of flocculation, flotation and agglomeration. Adsorption characteristics of the drug also have been found to have a significant effect on the dissolution of certain drugs.

Effect of Particle Size on Dissolution—Equation 3 shows a direct relationship between the surface area of the drug and its dissolution rate. Since the surface area increases with decreasing particle size, higher dissolution rates may be achieved through reduction of the particle size. This effect has been highlighted by the superior dissolution rate observed after *micronization* of certain sparingly soluble drugs as opposed to the regularly milled form. Micronization increases the surface area exposed to the dissolution medium and, hence, improves the rate of dissolution.

Several investigations have demonstrated an increased absorption rate for griseofulvin after micronization. Similar effects have been reported for chloramphenicol, tetracycline salts, sulfadiazine and norethisterone acetate. In the case of chloramphenicol, studies showed that formulations containing smaller particles (50 to 200 μm) were absorbed faster than formulations containing larger particles (400 to 800 μm). Figure 5[3] presents the effect of particle size differences on the dissolution rate of phenacetin and phenobarbital.

It should be recognized, however, that the mere increase in the surface area of the drug does not always guarantee an equivalent increase in dissolution rate. Rather, it is the in-

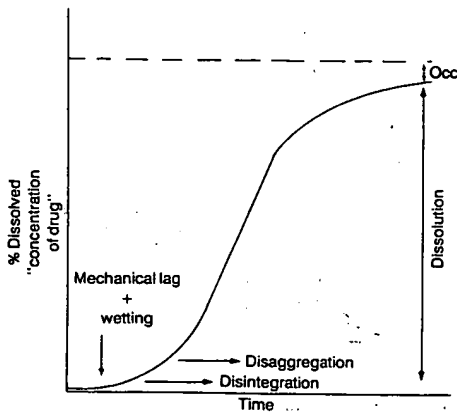

Fig 4. The S-shaped dissolution curve of solid dosage forms.[2]

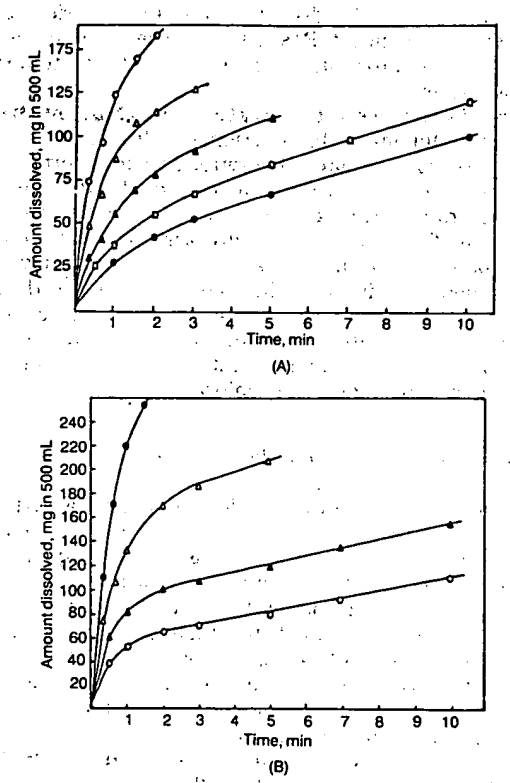

Fig 5. Effect of particle size on the dissolution rate of drugs from solid dosage forms.[3]

(A) *Key:* (Phenacetin) ○ particle size: 0.11–0.15 mm; △ particle size: 0.15–0.21 mm; ▲ particle size: 0.21–0.30 mm; □ particle size: 0.30–0.50 mm; ● particle size: 0.50–0.71 mm. (B) *Key:* Phenobarbital ● particle size: 0.07–0.15 mm; △ particle size: 0.15–0.25 mm; ▲ particle size: 0.25–0.42 mm; ○ particle size: 0.42–0.71 mm.

crease in the *effective* surface area, or the area exposed to the dissolution medium, and not the absolute surface area, that is directly proportional to the dissolution rate.

Physical properties of the drug particles other than size also affect indirectly the effective surface area by modifying the shear rate of the fresh solvent that comes in contact with the solid. These properties include the particle shape and the density.

Another mechanism by which the reduction in particle size improves dissolution is through the enhancement of the drug solubility (c_s). It should be pointed out that Eq 3 has an inherent limitation in assuming that c_s is independent of the particle size. Actually c_s and the surface areas can be correlated by the Ostwald-Freundlich equation

$$\ln S = \frac{2M\gamma}{\rho RT}\frac{1}{r} = \frac{\alpha}{r} \qquad (10)$$

where M is the molecular weight, ρ is the density, γ is the interfacial tension or surface free energy of the solid, r is the radius of the particle and T is the temperature.

From Eq 10

$$S = S_\infty \cdot e^{\alpha/r} \qquad (11)$$

The equation shows that the solubility is inversely proportional to particle radius. Therefore, S could be viewed as the solubility of the microparticles and S_∞ as the solubility of the macro particles. However, it is obvious that the particle radius has to be reduced to a microlevel before it can effect a change in solubility. This extreme reduction in particle size usually cannot be achieved through regular milling or even micronization procedures and, therefore, other methods have been recommended. One of these involves formation of a *solid-solution* or *molecular dispersion* where the molecules of the sparingly soluble drug either are dispersed interstitially in a water-soluble drug or replaced in its crystal lattice. Another technique, which also produces extremely small particles but still larger than the ones produced by solid solution, is by dispersion of the drug into a soluble carrier such as polyvinylpyrrolidone (PVP) solution. These techniques usually are employed for the enhancement of dissolution rate of insoluble drugs.

Effect of the Crystalline State of the Drug on Dissolution—The solid phase characteristics of drugs, such as amorphicity, crystallinity, state of hydration and polymorphic structure, have been shown to have a significant influence on the dissolution rate. For example, it was shown that the amorphous form of novobiocin has a greater solubility and higher dissolution rate than the crystalline form. Blood-level studies confirmed such findings where administration of the amorphous form yielded about 3 to 4 times the concentration compared to the administration of the crystalline form. Similar differences were demonstrated for griseofulvin, phenobarbital, cortisone acetate and chloramphenicol.

Factors Relating to the Solid Dosage Form

The effects of various formulations and manufacturing processing factors on the rate of dissolution and the bioavailability of the active ingredients from tablets and capsules have been well documented by several investigators since the early 1960s. Although the magnitude and significance of these effects must be determined individually for each tablet or capsule product, the following discussion of past and current findings certainly can serve as a guideline for the pharmaceutical scientist, especially during the initial stages of formulation design and product development.

Effect of Formulation Factors on Tablet Dissolution Rate—It has been shown that the dissolution rate of a pure drug can be altered significantly when mixed with various adjuncts during the manufacturing process of solid dosage forms. These adjuncts are added to satisfy certain pharmaceutical functions such as diluents (fillers), dyes, binders, granulating agents, disintegrants and lubricants. Generically identical tablet and capsule products, manufactured by different pharmaceutical houses, were found to exhibit signi[ficant] cant differences in dissolution rates for their active ingredient[s]. In certain cases, several studies showed that poor tablet an[d] capsule formulations have been shown to cause a marke[d] decrease in bioavailability and impairment of the clinic[al] response. Such findings during the sixties, especially in th[e] case of digoxin and tolbutamide tablets, as well as chloram[-] phenicol and tetracycline HCl (all lifesaving drugs), were th[e] triggering factors that compelled the drug-regulatory age[n]cies and compendial authorities to institute the dissolution test as a legal requirement for most solid dosage forms.

Diluents and Disintegrants—Levy, in 1963, studied th[e] effect of starch, the most commonly used diluent, on the ra[te] of dissolution of salicylic acid tablets manufactured by th[e] dry, double-compression process (Fig. 6[4]). Increasing th[e] starch content from 5 to 20% resulted in a dramatic increas[e] in the dissolution rate (almost threefold). This was attrib[-] uted to better and more thorough disintegration. Later, how[-] ever, Finholt suggested that the hydrophobic drug crystal[s] acquire a surface layer of fine starch particles that imparts [a] hydrophilic property to the granular formulation and thereby increases the effective surface area and hence the dissolution rate.

Effect of Binders and Granulating Agents on Dissolu[-] tion—Differences in binders used for tolbutamide tablet[s] resulted in variable dissolution characteristics and differences in the hypoglycemic effects observed clinically. Wet granula[-] tion, in general, has been shown to improve dissolution rate[s] of poorly soluble drugs by imparting hydrophilic properties to the surface of the granules. Solvang and Finholt showed that phenobarbital tablets granulated with gelatin solution dis[-] solved much faster in human gastric juice than those prepared with sodium carboxymethylcellulose or polyethylene glycol 6000 as a binder. They suggested that gelatin imparts hydro[-] philic characteristics to the hydrophobic drug surface, whereas polyethylene glycol forms a complex with poor solubility and sodium carboxymethylcellulose is converted to its less soluble acid form in low pH gastric juice (Fig 7[5]).

Effect of Lubricants on Dissolution—Levy and Gumtow investigated the effects of different types of lubricants on the dissolution rate of salicylic acid tablets. They found that magnesium stearate, a hydrophobic lubricant, tends to retard the dissolution rate of salicylic acid tablets, while a water-soluble surface-active lubricant, sodium lauryl sulfate, enhanced the dissolution rate significantly (Fig 8[6]). In[-] vestigating the mechanism of retardation, they suggested that hydrophobic lubricants, such as magnesium stearate, alumi[-] num stearate, stearic acid and talc, decrease the effective drug-solvent interfacial area by changing the surface charac[-] teristics of the tablets which results in reducing its wettability, prolonging its disintegration time and decreasing the area of the interface between the active ingredient and solvent. The

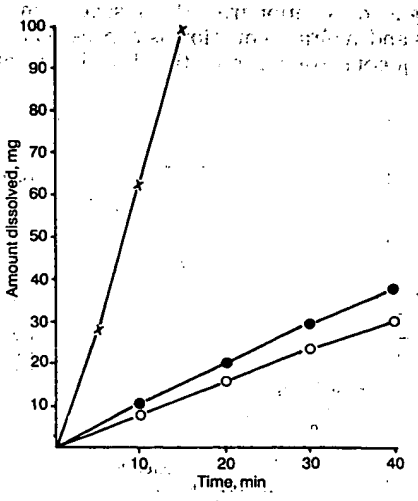

Fig 6. Effect of starch content on dissolution rate.[4]
Key: ○, 5%; ●, 10%; ×, 20% starch in granules.

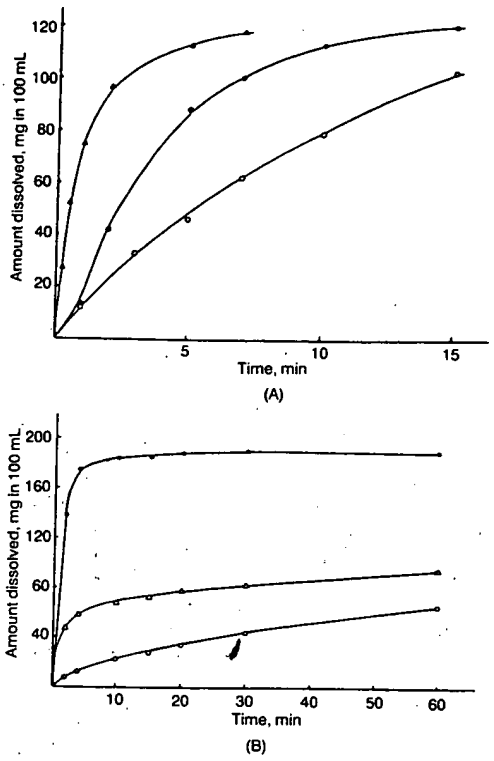

Fig 7. Effect of binders and granulating agents on dissolution rate of tablets.[5]

(A) Rate of dissolution of phenacetin from powder, granules and tablets in diluted gastric juice (surface tension 42.7 dynes cm.$^{-1}$, pH 1.85). *Key:* ○, phenacetin powder; ▲, phenacetin granules; ●, phenacetin tablets. (B) Dissolution rate of Phenobarbital Tablets in Diluted Gastric Juice (surface tension 39.4 dynes cm^{-1}, pH 1.50). *Key:* ● Gelatin Binder, △ CMC, ○ Polyethylene glycol 6000.

enhancing effect of sodium lauryl sulfate, on the other hand, was suggested to be due, in part, to an increase in the microenvironment pH surrounding the sparingly soluble weak acid and to increased wetting and better solvent penetration into the tablets and granules as a result of lowering the interfacial tension between the solid surface and the solvent. The fact that sodium lauryl sulfate is a water-soluble lubricant was not considered a factor in improving the dissolution rate of the tablet, since sodium stearate, another water-soluble lubricant, was found to have a retarding effect on the dissolution rate.

Effects of the Processing Factors on Dissolution Rates of Tablets—The many processing factors used in tablet manufacturing greatly influence the dissolution rates of the active ingredients. The method of granulation, the size, density, moisture content and age of the granules, as well as the compression force used in the tableting process, all contribute to the dissolution-rate characteristics of the final product.

Method of Granulation

Studies have shown that the granulation process, in general, enhances the dissolution rate of poorly soluble drugs. The use of fillers and diluents, such as starch, spray-dried lactose and microcrystalline cellulose, tend to increase the hydrophilicity of the active ingredients and improve their dissolution characteristics. In this regard, the wet granulation procedure traditionally was considered as a superior method compared to the dry or double compression procedure. With the advent of newer tableting machines and materials, however, it became more evident that the careful formulation and proper mixing sequence and time of adding the several ingredients are the main criteria that affect the dissolution characteristics of the tablets and not the method of granulation per se. Figure 9[7] shows the effect of different granulation methods on the dissolution rate of tablets.

Effects of Compression Force on Dissolution Rate

In his early studies of the physics of tablet compression, T Higuchi (1953), pointed to the great influence of the compressional force employed in the tableting process on the apparent density, porosity, hardness, disintegration time and average primary particle size of compressed tablets. There is always a competing relationship between the enhancing effect due to the increase in surface area through the crushing effect and the inhibiting effect due to the increase in particle bonding that causes an increase in density and hardness and, consequently, a decrease in solvent penetrability. The high compression also may inhibit the wettability of the tablet due

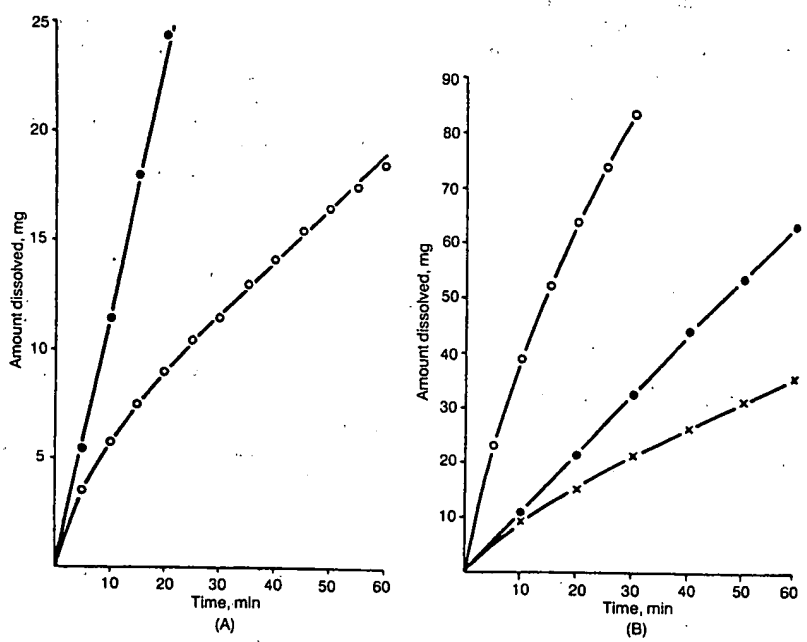

Fig 8. Effect of lubricant on the dissolution rate of tablets.[6]

(A) Effect of magnesium stearate on dissolution rate of salicylic acid from rotating disks made from fine salicylic acid powder. *Key:* ○, 3% magnesium stearate; ●, no lubricant added. (B) Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets (formula A). *Key:* ×, 3% magnesium stearate; ●, no lubricant; ○, 3% sodium lauryl sulfate.

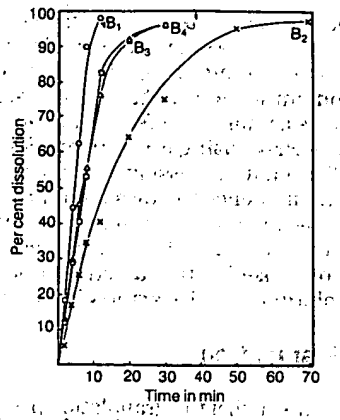

Fig 9. Effect of manufacturing process on the dissolution rate of tablets.[7]

Key: B_1 Direct compression with spray dried lactose; B_2 Wet granulation with ethylcellulose and lactose; B_3 Acacia mucilage and lactose; B_4 Starch paste and lactose.

to the formation of a firmer and more effective sealing layer by the lubricant under the high pressure and temperature that usually accompanies a strong compressive force (Fig 10[4]).

The curve profile of the compressive force of the tablet versus dissolution rate can take one of several shapes, as is observed in Fig 11[8].

Modified-Release Dosage Forms

Since the early 1950s, pharmaceutical preparations with controlled-release characteristics have been introduced with the purpose of optimizing the bioavailability through the modulation of the time course of the drug concentration in the blood. Such designed control is intended to complement the pharmacological activity of the medicament in order to achieve better selectivity and/or longer duration of action. This adds an extra dimension to the traditional functions of the dosage form being a mere vehicle for drug storage, portability and administration.

Modified-release dosage forms is a term used by the compendia to describe those dosage forms for which the drug-release characteristics versus time and/or conditions at the site of dissolution are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments or compressed tablets and capsules. At present, three types of modified-release dosage forms are described by USP. Procedures for the laboratory

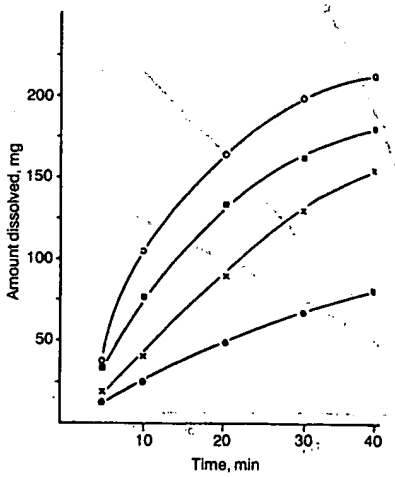

Fig 10. Effect of precompression pressure on the dissolution rate of salicylic acid contained in compressed tablets.[4]

Key: ●, 715 kg; ×, 1430 kg; ■, 2860 kg; ○, 5730 kg pressure per cm.² (Average of five tablets each, formula D.)

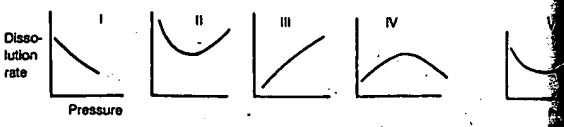

Fig 11. Different types of relations between compression[illegible] tablets and dissolution rate.[8]

evaluation of the behavior of modified-release dosag[illegible] are included in the USP in Section 724, *Drug Relea*[illegible] have been modified and expanded in supplements. *Drug Release* section five different apparatuses are do[illegible] in addition to the inclusion of Apparatuses 1 and [illegible] Section 711, *Dissolution.*

Delayed-release dosage forms are defined as tho[illegible] release a drug (or drugs) at any time other than prompt[illegible] administration. Enteric-coated products are an exam[illegible] such dosage forms. In order to evaluate delayed-rele[illegible] teric-coated) dosage forms, the USP uses two methods[illegible] B, which are carried out at 37 ± 0.5°. Both methods [illegible] use of the apparatus specified in the monograph for th[illegible] age form (*eg*, Aspirin Delayed-release Tablets, appar[illegible] 100 rpm) and expose the dosage units first to 0.1*N* hydr[illegible] ric acid and then to a pH 6.8 buffer in order to measur[illegible] release. The same acceptance tables are used for both[illegible] ods (limit of 10% dissolved drug in the acid after 2 hours[illegible] dissolved drug in the buffer after 45 minutes; three[illegible] testing provided).

Extended-release dosage forms (popularly kno[illegible] timed-release or sustained-release) are defined as thos[illegible] allow at least a twofold reduction in dosing frequen[illegible] compared to the drug presented in a conventional form[illegible] solution or a prompt drug-releasing conventional solid d[illegible] form.

Two procedures using different apparatus variation[illegible] employed to evaluate extended-release dosage fo[illegible] Apparatus 3 is an assembly that consists of a cylindrica[illegible] bottom vessel that accommodates a glass reciprocating [illegible] der whose ends are closed with a polypropylene mesh sc[illegible] The dosage unit is placed inside the reciprocating cylind[illegible] the release of drug into the solvent within the cylin[illegible] measured.

Apparatus 4 uses a flow-through cell with a filter sy[illegible] through which the dissolution medium is pumped. Ther[illegible] two different cells, a small and a large cell for tablets [illegible] capsules, and tablet holders for the small and large [illegible] Procedures that use either Apparatus 3 or 4 are carried o[illegible] 37 ± 0.5° and use the same three-stage acceptance criter[illegible] the interpretation of results.

Transdermal delivery systems are those systems[illegible] signed to deliver drugs by passage from the dosage f[illegible] through the skin to be available for distribution via the [illegible] temic circulation. An example of this kind of system is [illegible] nicotine patch.

In order to evaluate the drug release behavior of trans[illegible] mal delivery systems, three different apparatus systems [illegible] used. Apparatus 5 uses the paddle and vessel from Sec[illegible] 711, *Dissolution* Apparatus 2, and adds a stainless-steel [illegible] assembly to hold the transdermal system to be evaluated at[illegible] bottom of the vessel. Apparatus 6 uses the vessel assem[illegible] from Apparatus 1, *Dissolution*, except that the basket [illegible] shaft are replaced with a stainless steel cylinder stirr[illegible] element. At the beginning of a measurement, the dosage u[illegible] is affixed to the cylinder. Apparatus 7 uses solution cont[illegible] ers in which a specifically designed disc sample holder may[illegible] made to reciprocate. The procedures using Apparatuses [illegible] and 7 are all carried out at 32 ± 0.5° (since the deliv[illegible] systems are used on the skin) and yield results whose interp[illegible] tation is made using the same three-stage acceptance criter[illegible]

Dissolution Apparatus Design

As the concept of dissolution developed in importance d[illegible] ing the last several decades, the methods and techniques us[illegible]

n the *in vitro* procedure have evolved considerably from a mple, rudimentary apparatus that can be built from everyday boratory tools to a highly sophisticated, microprocessor-ontrolled and fully automated instrument. The various dis-olution apparatuses and techniques usually are classified ccording to their associated hydrodynamics.

Two general categories are recognized: the beaker meth-ds and the open flow-through compartment system.

The design of the apparatus affects the dissolution results hrough a number of factors. These include the geometry nd structure of the container, the type and intensity of agita-ion as well as the composition and volume of the dissolution edium. These factors, in turn, affect the abrasion rate of he intact solid dosage form on the particles, the dispersion of he disintegrated particles, the homogeneity of the dissolution luid and, finally, the reproducibility of the system from run to un.

Beaker Methods

These include all closed-compartment systems with a forced onvection mixing mechanism, where a relatively large vol-me of the dissolution medium (200 to 2000 mL) is contained n a beaker or a flask and agitation is performed by some type f a stirring, rotating or oscillating mechanism. The two fficial apparatuses described in the USP belong to this cat-gory.

USP Apparatus 1 consists of a 1000-ml covered cylindrical essel made of glass or an inert material, a cylindrical 40-mesh tainless steel basket connected to a metallic drive shaft and a peed regulated motor. The assembly is placed in a water ath that permits a constant temperature inside the vessel of 7° ± 0.5° during the test. Each of six tablets or capsules is nserted into an individual basket, and the baskets are lowered nto the dissolution vessels containing the specific volume of he dissolution medium, usually distilled water or 0.1*N* HCl. iltered samples from the dissolution medium are collected at ertain time intervals for the determination of the amount of he active ingredient dissolved.

The USP Apparatus 2 assembly is similar to Apparatus 1, except that a metallic paddle, usually coated with an inert material, is used in place of the basket assembly. The paddle s formed of a blade welded to a shaft that can be connected to he speed regulated motor. The tablets or capsules are dropped freely to the bottom of the flask, and the paddle is otated at the specified speed.

For exact descriptions and specifications of the USP disso-ution apparatuses, and the appropriate interpretation of the dissolution results, the reader is referred to the USP Section 711, *Dissolution*.

Both USP Apparatuses 1 and 2 have to be calibrated before use utilizing two types of calibrators recommended by the USP, a disintegrating type (prednisone) and a nondisintegrat-ing type (salicylic acid). The tablets are available from the USP.

Nonofficial Methods

Although probably more than 100 different dissolution meth-ods have appeared in the literature, only a few have main-tained their popularity after the introduction of the compen-dial procedures. Some of these are described below.

Rotating Filter/Stationary Basket Method (Spin Filter)—One of the main disadvantages of the rotating basket method is the possibility of clogging either the basket screen, the filter assembly, or both. On the other hand, while the paddle method does not suffer from such a problem, the possibility of floating tablets and/or particles, as well as nonreproducible tablet locations at the bottom of the flask constitute distinct deficiencies. Shah *et al* designed a system that virtually eliminates most of the problems associated with the compendial procedures (Fig 12[9]). It consists of a magnetically driven rotating filter assembly and a 12-mesh wire-cloth basket in which the dosage form is placed. The sample is withdrawn through the spinning filter for analysis. The system provides uniform, mild, laminar and nonturbulent agitation that is essential for reproducible results. It also ensures a representative sample of the bulk fluid with minimum abrasion to the solid dosage form. Because of the wide mesh screen used for the basket and the constantly spinning filter, no possibility of clogging exists in the system. It has been criticized, however, because of its complexity and the long time needed for setting up and cleaning.

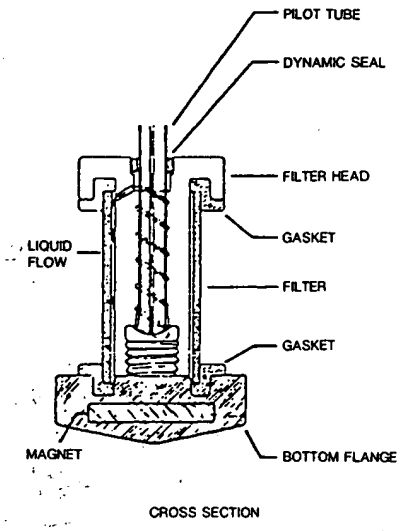

Fig 12. The rotating filter assembly.[9]

Rotating Bottle Method for Sustained-Release Formulations—This is probably the oldest dissolution apparatus originally developed during the late fifties for the determination of the dissolution rate of sustained release formulations. Newer versions have been in use; one of them was suggested in NF XIII, but has never been considered as an official method. The system consists of 12 small bottles (15 × 3 cm), attached to a horizontal shaft which rotates at a slow speed of 6 to 50 rpm. The whole assembly is placed in a constant temperature water bath. Each bottle contains 60 mL of dissolution fluid which is decanted through a 40-mesh screen after each sampling period and is replaced by fresh fluid. Usually five fluids of different pH are used: pH 1.2 for 1 hour, pH 2.5 for 1 hour, pH 4.5 for 1.5 hour, pH 7.0 for 1.5 hour and, finally, pH 7.5 for 2 hours for a total dissolution time of 7 hours.

Although a considerable data base has been generated using the rotating bottle method, most of the new sustained release formulations are tested by the compendial methods.

Open Flow-Through Dissolution Systems

In the beaker methods discussed above, (also known as closed-compartment methods) a forced convection type of agitation is generated in a relatively large vessel through a stirring, rotating or oscillating mechanism. In open flow-through methods (also known as open compartment methods), the dosage form is contained in a small vertical glass column with built-in filter through which a continuous flow of the dissolution medium is circulated upward at a specific rate from an outside reservoir using a peristaltic or centrifugal pump. The dissolution fluid usually is collected in a separate reservoir as it leaves the dissolution cell and, thereby, the dosage form is exposed continuously to fresh solvent (noncumulative mode), and a perfect sink condition is maintained. On the other hand, if a sink condition could be met easily using a limited volume of dissolution medium, the circulating fluid can be routed back to the original reservoir (cumulative mode).

The open-flow methods have several advantages over the beaker methods. Because the apparatus uses no stirring mechanism, the dosage form and drug particles are exposed continuously to a homogeneous, nonturbulent laminar flow that can be controlled precisely. All the problems of wobbling, shaft eccentricity, verticity, vibration, stirrer position, etc, simply do not exist. Also, the turbulent solvent flow associated with stirring mechanisms imparts variable degrees of physical abrasion of the solids but is avoided here.

Langenbucher's system consists of a cone-shaped dissolution cell with a filter attached to the top (Fig 13A and B[10]). The solvent is circulated from the bottom of the cone in which glass beads are placed to help maintain a laminar flow. Although a pulsating pump first was used to minimize filter

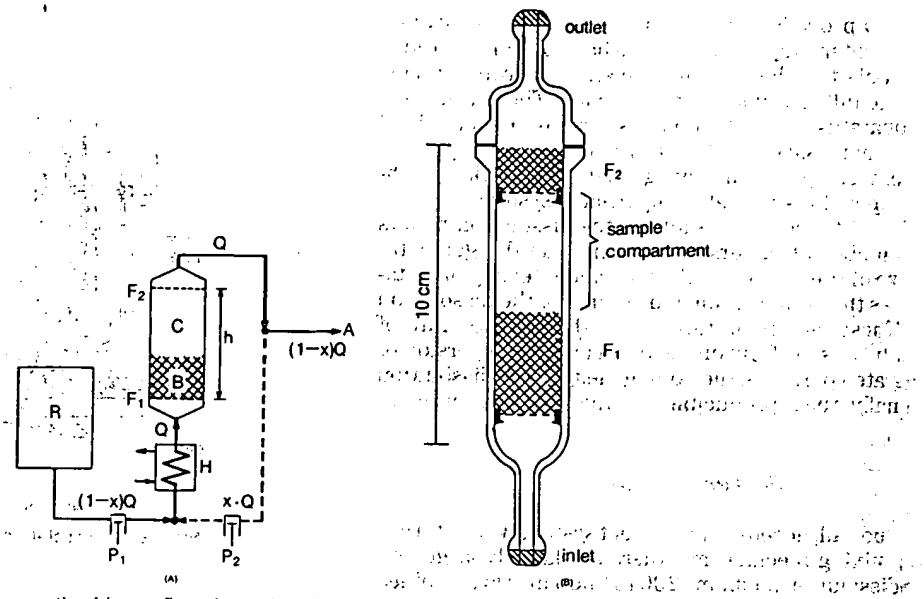

Fig 13. Column-type dissolution method (open flow-through system by Langenbucher).[10]

(A) Sketch of the column dissolution apparatus (schematic). *Key:* B, particle bed; C, cell; F_1, F_2, screens; H, heat exchanger; h, height of cell; P, volumetric pumps; R, liquid reservoir; x, circulation factor; Q, xQ, (1-x) Q, volumetric flow rates. (B) Specifications for the 4-cm² dissolution cell (drawn to scale). Inner cell diameter 22.6 mm. Height of sample compartment 40 mm. F_1: stainless steel sieve with 30-mm bed of glass beads 1 mm in diameter; F_2: 40-mesh stainless steel sieve with glass beads.

clogging, it was later shown that pulsation affects the dissolution rate significantly, and a centrifugal pump is preferred.

The open flow-through system, however, has its own disadvantages, the most important of which is the tendency of the filter to clog because of the unidirectional flow. Pressure tends to build near the end of the run and, in many cases, it is necessary to have built-in pressure transducers and a feedback mechanism to increase the pressure gradually in order to keep the flow rate constant. Another limitation, which should be pointed out, is the "pump" effect. Different types of pumps, such as the peristaltic and centrifugal varieties, have been shown to give different dissolution results.

A variation of the flow-through concept, is a closed column-type system which was introduced by Abdou *et al.* The system is a combination of a miniaturized rotating basket with a closed flow-through apparatus to keep the concentration of the drug at an acceptable range for quantitative determination (Fig 14[11]). The system is semiautomated in conjunction with an HPLC and is used for the determination of the dissolution rate of 0.1 mg fludrocortisone acetate tablets (Fig 13B[10]).

Automation in Dissolution Testing

Due to the large amount of testing required in determining the dissolution rate of drugs, automation of the process seemed almost a necessity and not simply a convenience to the analyst. Also, because of the modular nature of the dissolution apparatus, automation can be accomplished easily in different ways and by various techniques.

At present, however, the set up of the apparatus, media preparation and introduction of the dosage forms mostly are done manually. The rest of the process including the withdrawal of the sample, maintenance of a certain pH or of sink conditions, assay performance and data acquisition and calculations are, in most cases, fully automated. The automation process not only saves money, time and effort on the part of the analyst but more significantly it improves the overall reliability and enhances the reproducibility of testing procedures. Several approaches have been tried for the automation of dissolution such as those recommended by Bayer and Smith, Cioffi *et al* and Abdou *et al.* Details of these systems could be found in the indexed literature at the end of this chapter. Several commercial companies have also introduced semi- and fully automated dissolution systems. Some of these are Hanson Research's Dissolution System, Northridge CA; (Dissoette and Dissograph apparatuses), Technicon, Tarrytown NY (Sasdra apparatus) and Applied Analytical, Wilmington NC.

Millipore's Waters Chromatography Division has introduced a fully automated dissolution system using a Waters pump, detector and autosampler combined with a Hanson Research dissolution bath and sample transfer system (Fig 15). Samples are analyzed by HPLC, which provides better specificity than UV methods of analysis.

Hewlett-Packard manufactures a fully automated dissolution sampling and UV analysis system which can analyze samples from three dissolution baths.

Effects of Test Parameters on Dissolution Rate

Agitation

The relationship between intensity of agitation and the rate of dissolution varies considerably according to the type of agitation used, the degree of laminar and turbulent flow in the system, the shape and design of the stirrer and the physicochemical properties of the solid (Fig 15[12,13]). When a stirring device is used, such as the basket, paddle, rotating filter etc, the speed of agitation generates a flow that continuously changes the liquid/solid interface between the solvent and the drug in a way similar to the flow rate in the flow-through dissolution apparatus. In order to prevent turbulence and sustain a reproducible laminar flow, which is essential for obtaining reliable results, either the speed of agitation or the flow rate, depending on the type of apparatus employed, should be maintained at a relatively low level.

Study of the effect of agitation on the rate of heterogeneous reactions led to the empirical relationship between the rate of dissolution and the intensity of agitation

$$K = a(N)^b \quad (1)$$

where N is the speed of agitation, K is the dissolution rate and a and b are constants. If the dissolution process is diffusion controlled, the value of b should be 1 or close to 1 in accordance with the Nernst-Brunner film theory, which states that the film thickness is inversely proportional to the stirring speed. However, if the dissolution process is controlled purely by an interfacial reaction, the stirring speed would have no influence on dissolution and b should approach zero. If

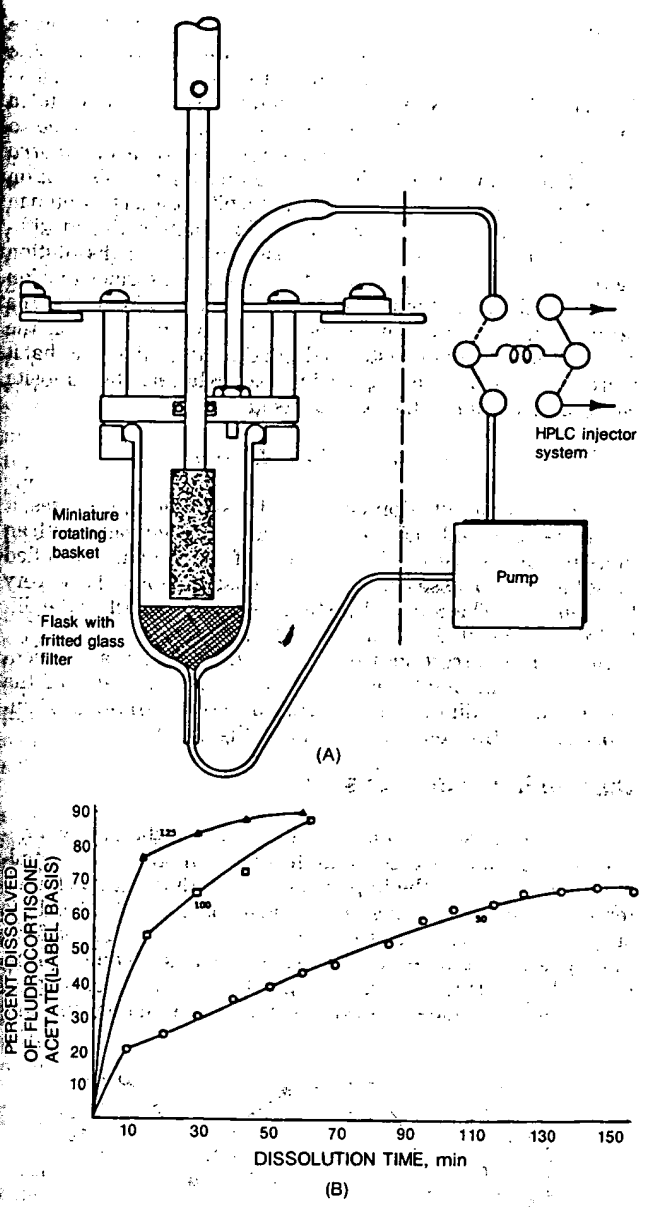

Fig 14. Apparatus for the determination of the dissolution rate of dosages with extremely small amounts of active ingredients.[11]

(A) Miniaturized USP basket apparatus, combined with a flow-through mechanism. (B) Comparison between the dissolution rate of fludrocortisone acetate at different rotation speeds. Each point is an average of six tablets of the same lot. *Key:* ○, 50 rpm; □, 100 rpm; and △, 125 rpm.

both processes are involved (such as dissolution of weak acids in buffer solution), the value of b should fall between 0 and 1. Also, as the nature of the flow changes from laminar to turbulent and the distance from the interface increases, the value of b also would vary according to the type of agitation utilized. Other factors that affect the correlation between agitation and dissolution rate include the density of the solid phase, the size and characteristics of the solid, the stirrer, the dissolution vessel and the heat of solution of the solute.

Temperature

Since drug solubility is temperature dependent, its careful control during the dissolution process is very important and should be maintained within 0.5°. Generally, a temperature of 37° always is maintained during dissolution determinations. The effect of temperature variations of the dissolution medium depends mainly on the temperature/solubility curves of the drug and excipients in the formulation (Fig 16[13,14]). For a dissolved molecule, the diffusion coefficient, D, is dependent

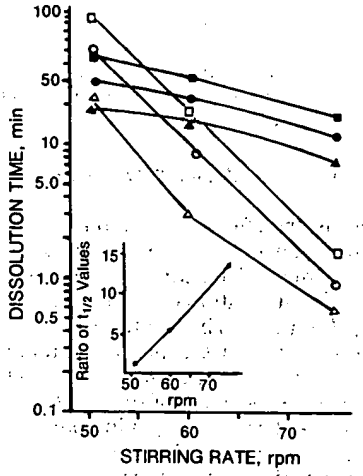

Fig 15. Effect of agitation on dissolution rate.[12,13]

Dissolution rate of aspirin from Type A[12] (open symbols) and Type B[13] (solid symbols) tablets as a function of stirring rate. Triangles, $t_{1/3}$; circles, $t_{1/2}$; squares, $t_{2/3}$. Inset: ratio of $t_{1/3}$ type B: type A tablets, as a function of stirring rate.

upon the temperature T according to the Stokes equation

$$D = kT/(6\pi\eta r) \qquad (13)$$

where k is the Boltzmann constant and $6\pi\eta r$ is the Stokes force for a spherical molecule (η is the viscosity in cgs or poise units and r is the radius of the molecule).

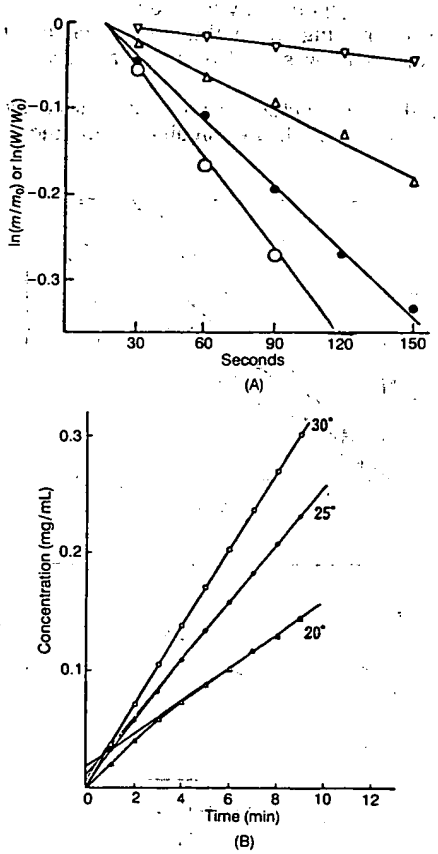

Fig 16. Effect of temperature on dissolution and disintegration rates of tablets.[13,14]

(A) Dissolution and disintegration curves according to Eqs 1 and 2 for position II of the USP basket. *Key:* ▽, dissolution at 10°; △, dissolution at 20°; ●, dissolution at 30°; and ○, disintegration at 5°.[14] (B) Dissolution of Phenobarbital anhydrate at various temperatures (at 300 rpm).[13]

Dissolution Medium

The selection of the proper fluid for dissolution testing depends largely on the solubility of the drug, as well as mere economics and practical reasons.

pH of the Dissolution Medium

Great emphasis and effort was first placed on simulating *in vivo* conditions, especially pH, surface tension, viscosity and sink condition. Most of the early studies were conducted in 0.1*N* HCl or buffered solutions with a pH close to that of the gastric juice (pH ~ 1.2). The acidic solution tends to disintegrate the tablets slightly faster than water and thereby it may enhance the dissolution rate by increasing the effective surface area. However, because of the corroding action of the acid fumes on the dissolution equipment, currently it is a general practice to use distilled water unless investigative studies show a specific need for the acidic solution in order to generate meaningful dissolution data. Another approach for avoiding the deleterious effects of hydrochloric acid is to replace it with acidic buffers, such as sodium acid phosphate, to maintain the required low pH.

Surface Tension of the Dissolution Medium

Surface tension has been shown to have a significant effect on the dissolution rate of drugs and their release rate from solid dosage forms. Surfactants and wetting agents lower the contact angle and thereby improve the penetration process of the matrix by the dissolution medium. Measurable enhancement in the dissolution rate of salicyclic acid from an inert matrix was reported by Singh *et al* when the contact angle, θ was lowered from 92° (water) to 31° (using 0.01% dioctyl sodium sulfosuccinate Fig 17[15]). The surface tension also was correspondingly lowered from 60 to 31 dynes/cm. The same findings were obtained in benzocaine studies when polysorbate 80 was used as the surface active agent (Fig 17[15]).

Other studies conducted on conventional tablet formulations and capsules also showed significant enhancement in the dissolution rate of poorly soluble drugs when surfactants were added to the dissolution medium, even at a level below the critical micelle concentration, probably by reducing the interfacial tension. Low levels of surfactants were recommended to be included in the dissolution medium as this seemed to give a better correlation between the *in vitro* data and *in vivo* condition. Finholt and Solvang compared the dissolution behavior of phenacetin and phenobarbital tablets in human gastric juice to that in dilute hydrochloric acid with and without various amounts of polysorbate 80 in the dissolution medium. The data showed that both pH and surface tension have significant influence on the dissolution kinetics of oral drug studies. For example, they found that not only was the dissolution rate much faster in diluted gastric juice, but that increased with decreasing particle size, whereas the opposite was the case when 0.1*N* HCl was used.

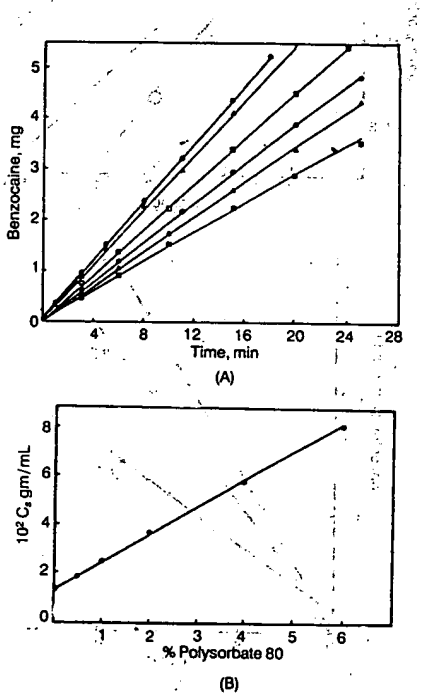

Fig 17. Effect of surfactants on dissolution rate.[15]
(A) Dissolution data for benzocaine in different concentrations of polysorbate 80 using the propeller-driven stirrer apparatus at a stirring speed of 150 rpm. *Key:* Polysorbate conc—○, 6%; △, 4%; □, 2%; ●, 1%; ▲, 0.5%; ■, 0%. (B) Solubilization data for benzocaine in different concentrations of polysorbate 80.

Viscosity of the Medium

In the case of diffusion-controlled dissolution processes it would be expected that the dissolution rate decreases with increase in viscosity. In the case of interfacial controlled dissolution processes however, viscosity should have very little effect. The Stokes-Einstein equation describes the diffusion coefficient *D* as a function of viscosity.

Braun and Parrott showed that the dissolution rate of benzoic acid is inversely proportional to the viscosity of the dissolution medium utilizing various concentrations of sucrose and methylcellulose solutions (Fig 18[16]).

Dissolution of Suspensions

Although most dissolution studies during the last two decades have concentrated on tablets and capsules, some studies have pointed to the importance of the dissolution characteristics of drugs administered in suspension. This hardly is surprising as suspensions are similar to the disintegrated form of tablets and capsules and, if dissolution has become a priority for these formulations, it is logical to extend its concept to suspensions. Indeed, several studies have shown that the

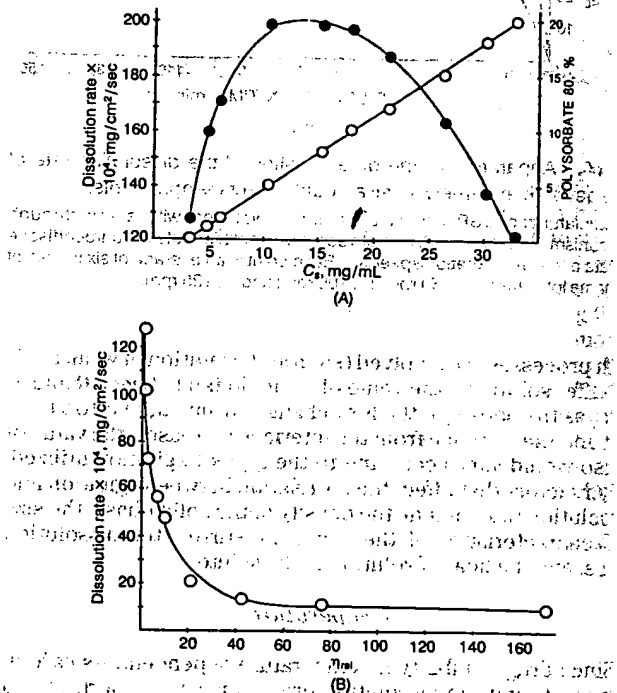

Fig 18. Effect of viscosity on dissolution rate.[16]
(A) Relationship of total solubility (C_s) of benzoic acid at 25° to dissolution rate and concentration of polysorbate 80. *Key:* ●, rate; and ○, concentration. (B) Relationship of viscosity to dissolution rate of benzoic acid in aqueous methylcellulose solutions at 25°.

absorption of several poorly soluble drugs administered in suspension formulations is dissolution-rate limited.

Such *in vivo/in vitro* correlation studies have confirmed the importance and the viability of dissolution rate determinations of suspensions as a discriminative test for rapid screening of new formulations and to control lot-to-lot variability within the same manufacturer and between different commercial manufacturers. In general, most of the dissolution apparatuses that have been described for tablets and capsules easily could be utilized for suspensions. The USP Apparatus 2 (Paddle) has been used frequently at a rotation speed between 25 to 50 rpm. However, the rotating filter apparatus by Shah, with the basket removed, has gained wide acceptance for suspensions since it provides mild laminar liquid agitation and it also functions as an *in situ* nonclogging filter. Sufficient volume of the dissolution medium should be used to maintain sink condition (about 900 to 1000 mL) and a temperature of 37° should be maintained. Rotation speeds of up to 300 rpm also have been used on occasion.

Dissolution of Topical Dosage Forms

Drug-release studies from gels, creams and ointments are becoming an important step both during the developmental stages of new formulations and as a routine quality control test for assuring the uniformity of the finished product. Also these studies often can provide useful information on some physicochemical parameters involved in the *in vivo* percutaneous absorption, such as the diffusion coefficient and the solubility of the drug in the specific vehicle used.

Although many investigators have conducted drug release rate studies from topical dosage forms, it appears that no single apparatus or procedure has yet emerged as the most favored, or to be accepted widely as a quasi-standard for others in the field. In reviewing the literature, however, it appears that two general techniques have been employed commonly. In the first, the sample is placed in direct contact with the receptor phase which acts as an aqueous sink, and the second utilizes various types of barriers to isolate the donor phase from the receiving medium. The barrier could be a dialysis membrane, a filter membrane, a membrane of animal origin or a polymer membrane.

Dissolution of Suppositories

Although most of the early work on suppositories has been concerned with their physical characteristics such as softening and liquefaction ranges, homogeneity, smoothness and neutrality, several reports appeared in the early literature pointing to the direct correlation between their efficacy and the release characteristics of the active ingredients. It has been reported that fatty bases, such as the popular cocoa butter, tend to release hydrophobic drugs, that are highly soluble in the oily base, very slowly. Emulsification of the fatty base significantly improved the drug-release rate. Incorporation of surface active agents was found to improve the release rate of water soluble drugs from the fatty suppository base dramatically.

Although many investigators have conducted extensive research on the release of drugs from suppositories, no single method or apparatus design has yet emerged as the standard procedure for the pharmaceutical laboratory. Many methods for the determination of the dissolution rate of suppositories are based on the dialysis technique where the suppository is placed in a dialyzing bag made of special membrane or cellophane material. The bag is placed in a beaker or wide mouth bottle containing a known volume of distilled water and the concentration of drug outside of the bag is measured as a function of time.

A slight variation of the basket method of the USP dissolution apparatus I also is used frequently. Hanson Research markets a basket apparatus for suppository dissolution testing. Hanson's modified basket uses slots instead of mesh to provide a suitable porosity. The use of such a basket avoids the blocking of the mesh opening of the regular USP basket when oil-based suppositories are used. The system also has the advantage of being capable of testing suppositories that float or have such low specific gravity that it interferes with the flow dynamics in the paddle method.

Developing a New Dissolution Method

Dissolution data, based on a discriminating and well thought out dissolution test is of tremendous value in the selection of the proper formulation. The dissolution test also can serve as a routine control mechanism to assure the uniformity of regular production batches. One of the first decisions to be made in the process of developing a new dissolution method is the choice of the apparatus. There are three types of apparatuses in the compendia, and several others are in current use by pharmaceutical companies, universities and regulatory agencies. Apparatuses differ, in great respect, with regard to the shape and geometry of the dissolution vessel, the type and intensity of agitation, the position of the dosage form, the dispersion of particles, the volume of the dissolution medium, the ability to change the solvent at a certain rate to maintain sink conditions and the reproducibility of the system. Wagner cautioned that the inherent variability in the dissolution method should be less than the inherent variability that can be tolerated in the product. He also recommended that the apparatus must be realistic scientifically, economically sound and have the ability to provide an effective hydrodynamic condition.

In deciding on which apparatus is to be used for testing, it should be emphasized that its features should allow for a convenient and reproducible mechanism for introducing the dosage form at a fixed position in the dissolution medium with minimal hydrodynamic disruption. The temperature of the dissolution medium should be maintained rigorously with minimum vibration and no localized overheated spots.

The dissolution apparatus also should allow for the maintenance of sink conditions by allowing for continuous exchange of the dissolution fluid with fresh solvent. The apparatus also should provide for the testing of various types of dosage forms with a convenient and reproducible sampling technique that results in a minimum disruption of the dosage form dissolving bed or the hydrodynamic condition of the dissolution medium. Automatic filtration mechanisms that are inserted in the dissolution fluid are preferred, as they avoid the removal of insoluble drug powder. Simple and rapid analytical methods should be used, as many drugs tend to degrade rapidly in dilute aqueous solutions.

In reviewing the above criteria for a sound dissolution apparatus, it easily could be recognized that the compendial dissolution methods 1 and 2 actually do not fair badly when compared to other available dissolution systems.

In general, if the compendial apparatus is to be used, 900 mL of distilled water with an agitation speed of 100 rpm for the rotating basket and 50 rpm for the paddle method is a good starting point. However, a check to determine if deaeration of the water is necessary has to be conducted. If such parameters prove to be inadequate, a slightly higher stirring rate may be tried. If not successful, the composition of the dissolution medium could be changed. Dilute hydrochloric acid or buffer systems of different pH could be used. In the case of enteric coated or sustained-release preparations, media pH change may be required during the test.

In regard to the quality-control aspect, it is advisable to set dissolution guidelines close to the expected performance of the selected formulation. The specification usually includes both DT_{50} and DT_{85} or DT_{85} (DT_x = time for dissolution of 50 or 85%) only. The specifications, however, can be altered as further production experience is obtained. Once the specification is finalized, any batch which does not comply should be reviewed completely to find the cause of its poor dissolution.

A knowledge of the dissolution rate of poorly soluble drug substances (intrinsic dissolution rate, $K = kD/h$ from Eq 3), is very useful in predicting whether their biological absorption

is dissolution limited or not. Such information is essential during the early stages of formulation of a new drug dosage form as it can point to a future bioavailability problem. Depending on how slow the intrinsic dissolution rate is, the formulator may choose to improve it by micronization, complex formation, derivatization or any of the other techniques generally utilized for enhancing the dissolution rate of insoluble drugs. The information also is very useful for improving existing formulations which have exhibited bioavailability problems.

For the determination of the intrinsic dissolution rate, most investigators compress the pure powdered drug under extremely high pressure in the absence of any additives. The resulting nondisintegrating disk then is transferred to any of the previously discussed dissolution apparatuses. Because of the nondisintegrating characteristic of the disk, the surface area essentially is constant during the entire duration of the test. This facilitates the calculation and interpretation of the results. Usually, the modified form of Noyes and Whitney equation, previously discussed is used as the basis for calculation.

Also, the effects of the various formulation factors as well as the key processing factors such as the compression force, mixing time and in-process storage conditions have to be determined. This will provide information on how critically these important variables have to be controlled during routine production.

Furthermore, appropriate stability studies should be conducted to establish what changes take place, if any, in the dissolution characteristics of the selected formulation after it has been held in stability storage for a reasonable period of time. Accelerated conditions (stress studies) also could be used for the same purpose. After the dissolution pattern of the selected formulation has been established, an *in vivo* study may be conducted to establish *in vitro/in vivo* correlation. It is advisable that these studies be conducted on humans and not on animals, since man will be the final vehicle for drug dissolution.

References

1. Abdou HM: *Dissolution, Bioavailability and Bioequivalence*, Mack Publ Co, Easton PA, 1989.
2. Carstensen TJ: *Dissolution—State of the Art 1982* (Proc 2nd WI Update Conf), Extension Services in Pharmacy, Univ of Wisconsin, Madison WI, 1982.
3. Finholt P. In Leeson LJ, Carstensen TJ, eds: *Dissolution Technology*, APhA, Washington DC, 108, 1974.
4. Levy G *et al.*: *J Pharm Sci 52:* 1047, 1963.
5. Solvang S, Finholt P: *Ibid 59:* 49, 1970.
6. Levy G, Gumtow RH: *Ibid 52:* 1139, 1963.
7. Marlowe E, Shangraw R: *Ibid 56:* 498, 1967.
8. Finholt P. Ref 3, p 134.
9. Shah A *et al.*: *J Pharm Sci 62:* 671, 1973.
10. Langenbucher F: *Ibid 58:* 1265, 1969.
11. Abdou HM *et al.*: *Ibid 67:* 1397, 1978.
12. Levy G *et al.*: *Ibid 56:* 1365, 1967.
13. Nogami H: *Chem Pharm Bull 17:* 499, 1969.
14. Carstensen TJ *et al.*: *J Pharm Sci 69:* 291, 1980.
15. Singh P *et al.*: *Ibid 57:* 959, 1968.
16. Braun R, Parrott E: *Ibid 61:* 175, 1972.

Bibliography

General

Abdou H: *Dissolution, Bioavailability and Bioequivalence*, Mack Publ Co, Easton PA, Chap 2, 1989.

Brunner E, Tolloczko S: *Z Phys Chem 35:* 283, 1900.

Crank J: *The Mathematics of Diffusion*, Oxford Univ Press, New York, 1956.

Dissolution—State of the Art 1982 (Proc 2nd WI Update Conf), Extension Services in Pharmacy, Univ of Wisconsin, Madison WI, 1982.

Edwards L: *Trans Faraday Soc 47:* 119, 1951.

Gibaldi M, Perrier D: *Pharmacokinetics*, Marcel Dekker, New York, 270, 281, 1974.

Hanson WA: *Handbook of Dissolution Testing*, Pharmacy Technology Publ, Springfield OR, 1982.

Higuchi T *et al.*: *JAPhA Sci Ed 42:* 194, 1953.

Higuchi T *et al.*: *Ibid 43:* 344, 1954.

Higuchi T, Lach J: *Ibid 43,* 465, 1954.

Hixson A, Crowell J: *Ind Eng Chem 23:* 923, 1931.

Leeson LJ, Carstensen TJ, eds: *Dissolution Technology*, APhA (Ind Pharm Technol Sec/Acad Pharm Sci), Washington DC, 1974.

Levy G: *J Pharm Sci 50:* 388, 1961.

Nelson KG, Miller KW. In Blanchard J, Sawchuk RJ, Brodic BB: *Principles and Perspectives in Drug Bioavailability*, S Karger, Basel, 1979.

Nernst V, Brunner E: *Z Phys Chem 47:* 52, 56, 1904.

Noyes AA, Whitney WR: *J Am Chem Soc 19:* 930, 1897.

Shenoy K, Chapman D, Campbell J: *Drug Stand 27:* 77, 1959.

Wagner JG: *Drug Intell Clin Pharm 4:* 137, 1970.

Wagner J, Pernarowski M: *Biopharmaceutics and Relevant Pharmacokinetics*, Drug Intell Publ, Hamilton IL, 1971.

Wurster DE, Taylor PW: *J Pharm Sci 54:* 670, 1965.

Particle Size

Hirschorn J, Kornblum S: *J Pharm Sci 60:* 445, 1971.

Levy G: *Am J Pharm 135:* 78, 1963.

Crystalline State of the Drug

Aguiar A *et al.*: *J Pharm Sci 56:* 847, 1967.

Poole J: *Curr Ther Res 10:* 292, 1968.

Formulation and Processing Factors for Tablet Formulations

Chowhan Z *et al.*: *J Pharm Sci 71:* 1371, 1982.

Levy G *et al.*: *Ibid 52:* 1047, 1963.

Marlowe E, Shangraw R: *Ibid 56:* 498, 1967.

Factors Relating to the Dissolution Apparatus and Test Parameters

Abdou H, Ast T, Cioffi F: *J Pharm Sci 67:* 1397, 1978.

Hanson W: *Handbook of Dissolution Testing*, Pharmacy Technology Publ, Springfield OR, 88, 1982.

Langenbucher F: *Pharm Acta Helv 49:* 187, 1974.

Pernarowski N. In Leeson L, Carstensen J: *Dissolution Technology*, APhA (Ind Pharm Technol Sec/Acad Pharm Sci), Washington DC, 1974.

Stavchansky S: *Dissolution—State of the Art 1982* (Proc 2nd WI Update Conf), Extension Services in Pharmacy, Univ of Wisconsin, Madison WI, 1982.

Intrinsic Dissolution Rate

Cartensen J, Musa M: *J Pharm Sci 61:* 223, 1972.

Tingstad J *et al.*: *Ibid 62:* 293, 1973.

Effect of Dissolution Medium, pH and Surface Tension

Felmeister A: *J Pharm Sci 61:* 151, 1972.

Singh P *et al.*: *Ibid 57:* 217, 1968.

Solvang S, Finholt P: *Ibid 59:* 49, 1970.

Automation in Dissolution Testing

Abdou H, Ast T, Cioffi F: *J Pharm Sci 67:* 1397, 1978.

Beyer W, Smith E: *Ibid 60:* 1556, 1971.

Cioffi F, Abdou H, Warren A: *Ibid 65:* 1236, 1976.

Shah A, Poet C, Ochs J: *Ibid 62:* 671, 1973.

Effects of Agitation on Dissolution Rate

Levy G, Leonard J, Procknal J: *J Pharm Sci 56:* 1365, 1967.

Modified-Release Dosage Forms

Pharmacopeial Forum, USP, Rockville MD, 2991-3000, May–Jun 1983.

Effect of Temperature

Carstensen J *et al.*: *J Pharm Sci 69:* 290, 1980.

Effect of Viscosity

Braun R, Parrott E: *J Pharm Sci 61:* 175, 1972.

Developing a New Dissolution Method

Wagner G: *Biopharmaceutics and Relevant Pharmacokinetics*, Drug Intelligence Publ, Hamilton IL, 110, 1971.

Sarapu A, Clark L: *J Pharm Sci 69:* 129, 1980.